

CHEMOTHERAPY AND MELANOMA

Malignant melanoma is a skin cancer that when left to grow to a deep proportion becomes metastatic has an increasing chance of becoming a fatal cancer. Melanoma is related to sun exposure. Dermatologists worldwide are trying to fight an epidemic of melanoma. Melanomas are increasing in prevalence. There can be an increase risk in families and those with fair complexions seem to be at a higher risk. Everyone is encouraged to have good sun protection and being married to a dermatologist means for us skin creams and cover-up. It is a topic of concern at the dinner table.

A recent article by Danson et al published in the prestigious Journal of Clinical Oncology looked at chemotherapy for treatment of metastatic melanoma.

Melanoma comprises of about one in every fifty cancers in the US. Its diagnosis is increasing. Usually surgery is the modality used when cancer is local. Once the cancer is metastatic the average survival is six to nine months. Systemic treatment such as chemotherapy is usually poor.

A variety of chemotherapies have been used. Dacarbazine has been the standard chemotherapy for melanoma. The response rate is about 15% - meaning in 85% of the patients cancer dose not respond to this chemotherapy. Even when response did occur it was usually incomplete and temporary. There are a variety of other chemotherapies that have been used.

Recently, Temozolomide has been used for a variety of tumors including brain tumors. It can be given orally which is PO and can penetrate the blood brain barrier and get into the brain. This is important since often melanomas do in fact spread to the brain.

Recently there was a randomized study that took three to five patients with melanoma and compared Temozolomide to Dacarbazine. There was an equivalent overall toxicity in survival in terms of progression free survival and quality of life. Also, patients with Temozolomide had seemed to have a lower incidence of brain relapse.

Of patients who had response to therapy, 10% with Temozolomide had brain relapse versus 43% with Dacarbazine. Interleukin, which is an immuno-agent, has been used with chemotherapy for melanoma for nearly 20 years.

Some have reported better disease free survival and survival. Thalidomide is an anti-angiogenic agent and can modify biologic properties in the body. It has been used Call or write as questions arise, Kaposi's sarcoma, myeloma and kidney cancer. Thalidomide has also been used for metastatic melanoma as a single agent.

Recently a study was reported in the Journal of Clinical Oncology that evaluated Temozolomide given either every eight hours, with Interferon Alpha B2, or with Thalidomide in metastatic melanoma.

Two centers in England that took care of patients with melanoma and provided patients including those who had no prior chemotherapy, full recovery from prior radiation and in general good bone marrow function. Patients were excluded if they were pregnant or nursing.

Patients were randomly allocated to eight-hourly Temozolomide, Temozolomide plus Interferon or Temozolomide plus Thalidomide.

Temozolomide was 200mg per meter squared for a total of five doses. On Temozolomide and Interferon, Temozolomide was 200mg per meter squared orally once a day for five days with Interferon Alpha B2, five MIU given subcutaneously every Monday, Wednesday and Friday. In Temozolomide with Thalidomide, Temozolomide was 150mg per meter squared for the first cycle then increased to 200mg

per meter squared for each subsequent cycle Thalidomide 100mg orally daily for 28 days. Treatment cycles were to be repeated every four weeks with good blood counts.

Patients were evaluated completely two weeks before receiving drugs; blood counts and other tests were performed. Between 1998 and 2001 181 patients were enrolled in the two studies. Fifty-nine were randomly allocated to 8 hourly Temozolomide, 62 patients with Temozolomide Interferon and 60 patients to Temozolomide Thalidomide. At the end of analysis in April 2002 eight patients on eight hourly Temozolomide, 10 patients on Temozolomide Interferon and 14 patients on Temozolomide and thalidomide remained alive at a median follow-up of 6 months – overall median survival for 8 hourly Temozolomide was 5.3 months compared to 7.7 months on Temozolomide and Interferon, and 7.3 Temozolomide and Thalidomide. The range of survival was 0.1 to 36.5 months. Progression free survival was similar in the three groups of patients treated. Of the 39 patients who responded the progression free survival was 11.7 months in the eight hourly Temozolomide, nine months in the Temozolomide and Interferon and 7.5 months in Temozolomide and Thalidomide. The overall duration of response in those responded was 2.4 to 21.2 months. The one-year survival was 18%, 26% and 24%. The two-year survival was 7%, 9% and 17% with eight hourly Temozolomide, Temozolomide and Interferon, Temozolomide and Thalidomide respectively.

The complete response was seen in 3% of patients with combination but in none of the patients receiving 8 hourly Temozolomide. Objective response was seen in 9% of the patients who received 8 hourly Temozolomide, 18% of the patients who received Temozolomide and Interferon, and 15% of the patients who received Temozolomide and Thalidomide. Overall, the response rate was 14.1% with 2.3% receiving complete responses. There were two deaths in which treatment was implicated. One was in the eight hourly Temozolomide and the other was Temozolomide and Interferon with bleeding into the brain metastases. Other toxicity in addition to anemia was nausea, vomiting, constipation, diarrhea, hair loss, and rash, those relating to lung, fever, infection, lethargy and liver and kidney function.

Twenty-one patients had brain metastases at the time of treatment. One patient had immunotherapy, neurosurgery and brain radiation, had brain metastases diagnosed and then no metastases to the brain at the end of treatment. Of 21 patients 8 received eight hour Temozolomide, six Temozolomide and Interferon and seven received Temozolomide and Thalidomide. All but one of the patients with brain metastases progressed on treatment.

Obviously, melanoma is a difficult disease to treat with immunotherapy or chemotherapy. Of course the authors noted there was “an urgent need to improve on existing treatment”. Only about 14% of the patients in this study responded to treatment which is similar to prior studies with a complete response of 2.3%.

The authors conclude, “There has been much interest in Temozolomide because it crosses the broad brain barrier, unlike Dacarbazine. In this study, the portion of patients known to have brain metastases at the commencement of treatment was small, (12% overall); only symptomatic patients would undergo a computed tomography scan of the head. There was only one responder in this group. There were eleven relapses in the brain in patients not known to have brain metastases at the start of treatment; more of these patients were in the combination arms, but this may be because these patients lived longer. It is difficult to draw conclusions from these small numbers but future trials should be designed to document the incidence and outcome of patients with brain metastases.”

“In conclusion, all three regimens were tested were well-tolerated and had comparable efficacy, although there was an indication of better tumor response and overall survival with combination arms. There was significantly less hematologic toxicity with Temozolomide plus Thalidomide, and this combination seems the most promising for future study.”

Our physicians with great experience in radiosurgery have used this more precise method of high dose per fraction-limited number of fraction radiation techniques for patients with melanoma.

We have seen a high control rate of the targeted area while radiosurgery is palliative in nature and may help stop bleeding, pain or other symptoms. Obviously, since chemotherapy can benefit only about 14% of patients than those temporarily, we must consider other options for those today.

Fifty-five patients with 97 tumors were treated using body radiosurgery in sites including the abdomen, adrenal, ankle, chest, groin, hip, liver, lung, lymph nodes, mediastinum, neck, pancreas, pre-sacral space, rib, shoulder, spine and spleen. The treated tumor volume ranged from 0.44 to 5,916cc, with a mean of 371.8cc. Dose per fraction ranged from 270 to 1000 rad (mean 601.1). The number of fractions ranged from 3 to 15 with a median of 5 treatments. The total dose delivered was from 2000 to 5000 rad (median of 3000 rad). Thirty-eight patients had prior chemotherapy.

At the time of our evaluation, eight patients were still alive. Twenty-one patients were evaluated post-treatment with contrast-enhanced CT scan. Of those cancers evaluated, 5% disappeared, 29% decreased in size, 53% showed cessation of growth and 13% progressed. Therefore, 87% of the cancers evaluated were controlled. (Control is defined as cessation of growth, shrinkage or disappearance of the tumors in the treated field.) Progression-free survival for the 18 patients that showed disease control was calculated to be 8.9 months from first radiosurgery treatment and 21.0 months from time of diagnosis.

We have seminars open to the public to discuss treatment options. We also have multi-disciplinary panels of physicians to review films, reports and medical history. We have a cancer hot line to answer questions: 212-CHOICES and as well have an e-mail address: gil.lederman@rsny.org.